

**REMARKS**

Pursuant to the entry of the instant amendment, claims 1, 2, and 4-24 are presently pending. In an effort to expedite prosecution and simplify the issues at hand, Applicants have herewith amended the claims as follows:

- Independent claims 1 and 2 have been amended to include the limitations of claim 3, now canceled, more particularly the step of adjusting the pH of the plasma fraction to “a value between pH 4.7 and pH 5.3”.
- Independent claims 1 and 2 have been amended to specify that the process results in the formation of precipitate comprising “70% to 99% of the initial amount of fibronectin” present in the original plasma fraction.
- Independent claims 1 and 2 have been further amended to define the contents of the plasma fraction, the precipitate, and the supernatant so as to address issues of indefiniteness and antecedent basis.
- Dependent claims 9, 15, and 16 have also be amended to address issues of indefiniteness and antecedent basis.
- New claims 19-24 present additional features of the invention, such as the preferred temperature (e.g., 4° C to 35° C, more preferably 20° C to 25° C (i. e., room temperature)) and the optimum level of fibronectin depletion (e.g., at least 90%).

Support for these amendments is found in the specification as originally filed, particularly in the following sections of the application as published on August 30, 2007 (US-2007-030330 A1):

- “The addition of precipitation reagents and high salt concentrations increase the danger that the desired product (e.g. von Willebrand factor) is partially precipitated out of the supernatant as well.” [0011], emphasis added;
- “The process according to the invention can be carried out within a wide temperature spectrum, e.g. from about 1° C to 37° C. Preferred temperature ranges are 4 to 35° C, more preferably 10 to 30° C, most preferably the process is carried out from 20 to 25° C.” [0027], emphasis added;

- “The fibronectin concentration in the plasma fraction can be reduced by at least 50% by means of the inventive process for removing fibronectin from plasma fractions. The fibronectin concentration is preferably reduced in the plasma fraction by 70 to 99%, more preferably by 80 to 99%, most preferably by 90 to 98% or by 95 to 98%.” [0029], emphasis added;
- “Having separated the precipitate which contains fibronectin from the plasma fraction, further purification steps may follow to purify at least one coagulation factor.” [0031] emphasis added;
- From Example 2: “90% of fibronectin could be removed with a loss of only 5% of target protein vWF.” [0056], emphasis added.

Thus, Applicants respectfully submit that no new matter has been added. However, Applicants reiterate that these amendments are presented solely for the purpose of expediting prosecution and should not be construed as Applicants’ agreement with or acquiescence to the grounds of rejection previously set forth.

Turning to the outstanding Office Action of May 27, 2008:

*Rejections under 35 U.S.C. § 112, First Paragraph*

Claims 1, 2, and 4-18 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement. According to the Examiner, while the specification enables the formation of a precipitate from a plasma fraction at a pH between 4.7 and 5.3, it does not reasonably provide enablement for the formation of a precipitate “at any pH below 5.4”. More particularly, the Examiner asserts that given the unpredictability in the art, coupled with the limited guidance in the specification and limited scope of the working examples, undue experimentation would be required to ascertain exactly which values below a pH of 5.4 would cause the plasma fraction to form a precipitate.

Applicants respectfully disagree and remind that the test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, provided it is merely routine. Nevertheless, in an effort to expedite prosecution, Applicants have amended

independent claims 1 and 2 to specify a pH value between 4.7 and 5.3. Applicants respectfully submit that the instant amendment renders moot the Examiner's enablement concerns and that the scope of the claims as amended is commensurate with the alleged scope of enablement. Accordingly, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection of claims 1, 2, and 4-18 stand rejected under 35 U.S.C. § 112, first paragraph, in view of the amendments and remarks herein.

*Rejections under 35 U.S.C. § 112, Second Paragraph*

Claims 1-18 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner objects to the clarity and precision of the pending claims as follows:

- (i) With respect to claims 1 and 2 *et seq.*, the Examiner objects to the claims for failing to clearly connect the goal of the preamble (e.g., a process for separating fibronectin from a plasma fraction or producing a composition containing a coagulation factor) with the recited steps (e.g., adjusting the pH, separating the precipitate formed);
- (ii) With respect to claim 7, the Examiner objects to the term "fibronectin precipitate" as lacking clear antecedent basis support in any of the preceding claims;
- (iii) With respect to claim 9, the Examiner objects to the term "the concentration of NaCl or KCl" as lacking clear antecedent basis support in any of the preceding claims; and
- (iv) With respect to claim 15, the Examiner objects to the term "solvent/detergent treatment" as being unclear.

The test for indefiniteness is whether one of ordinary skill in the art would understand the metes and bounds of the claim, when read in light of the specification and in the context of the prior art. Thus, claim language cannot be analyzed in a vacuum but must be interpreted in light of the specification, the teachings of the prior, and the reasonable interpretation given by one of ordinary skill.

In this case, regarding item (i), to expedite prosecution, Applicants have amended claims 1 and 2 to more directly connect the claimed method steps with the goals of the preamble, thereby rendering moot the Examiner's clarity concerns.

Regarding item (ii), to expedite prosecution, Applicants have amended claim 1 to provide explicit support for the element of a “fibronectin precipitate”, thereby rendering moot the Examiner’s antecedent basis concerns.

Regarding item (iii), to expedite prosecution, Applicants have revised the wording of claim 9 to address the Examiner’s antecedent basis concerns (e.g., “the plasma fraction initially contains NaCl or KCl at a concentration of 100 – 200 mM”).

Regarding item (iv), to expedite prosecution, Applicants have amended claim 15 to refer to “treatment with a solvent and/or a detergent”, thereby rendering moot the Examiner’s clarity concerns.

Applicants respectfully submit that the claims so amended meet the threshold requirements for clarity and precision set forth in 35 U.S.C. § 112, second paragraph. As such, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections of claim 1, 2, and 4-18 under 35 U.S.C. § 112, second paragraph in view of the amendments and remarks herein.

*Rejections under 35 U.S.C. § 102*

*Zykova et al.:*

Claims 1, 3-5, and 10-11 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Zykova et al. (1983) (hereinafter referred to as “Zykova”).

According to the Examiner, Zykova teaches a method of precipitating fibronectin at a pH of 5.0. The Examiner thus concludes that Zykova anticipates the invention of the pending claims.

Applicants respectfully disagree with the Examiner’s characterization of the Zykova reference. It is well settled that in order for a reference to anticipate, it must disclose each and every element of the pending claims. In this case, Zykova discloses the preparation of fibronectin from bovine blood serum, obtained by means of affinity chromatography on collagen separation, through “differential salting out”, using high concentrations of ammonium sulfate ranging from 0.8 to 2.0 M (or 800 to 2000 mM) at a pH of 5.0. In contrast, the pending claims require low salt concentrations, using a plasma fraction that is “characterized by an ionic strength

below 500 mM”. Thus, in that Zykova fails to disclose each and every element of the claim, it cannot serve to anticipate. As such, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections of claims 1, 4-5, and 10-11 under 35 U.S.C. § 102(b) in view of the amendments and remarks herein.

Wallace et al.:

Claims 1-5, 6, 8, 10-11, 14, 16, and 18 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Wallace et al. (USPN 4,341,764, referred to hereinafter as “Wallace”).

According to the Examiner, Wallace teaches a method of preparing fibronectin and an anti-hemophilic factor from blood plasma comprising the steps of acidifying a solution of blood plasma to a pH sufficient to form an acid precipitate containing fibronectin (e.g., a pH of about 5.0) and further isolating fibronectin from the precipitate and an anti-hemophilic factor from the remaining solution. The Examiner thus concludes that Wallace anticipates the invention of the pending claims.

Applicants respectfully disagree with the Examiner’s characterization of the Wallace reference. Applicants further submit that the claim amendments presented herewith in order to expedite prosecution render moot the Examiner’s assertion of anticipation.

It is well settled that in order for a reference to anticipate, it must disclose each and every element of the pending claims. In this case, Wallace discloses a complex, multi-step process for the preparation of fibronectin and fibronectin substitutes from an acid-chill precipitate. As shown in Figure 2, the Wallace method consists of several steps, each aimed at the production of precipitates which can serve as fibronectin substitutes. The initial step involves solubilizing a cryoprecipitate in an aqueous medium, preferably water, and then acidifying the solution to a pH within the range of 5.0 to 6.8, more preferably 5.8 to 6.4. This solution is then centrifuged to give a first acid precipitate and an antihemophilic factor (AHF) solution. This first acid-precipitate has a fibronectin-like activity [col. 3: 14-21]. In a second step, the AHF solution is chilled to a temperature of about 2° to 20° C, more preferably about 2° to 7.5° C, then further centrifuged to obtain a chill-precipitate which can be used as a fibronectin substitute [col. 3: 24-35].

Thus, the Wallace process involves the use of several distinct steps, including multiple centrifugation steps, to obtain a purified fibronectin substitute precipitate. However, Wallace requires further cooling steps to precipitate remaining fibronectin and even then only permits the capture of greater than 50%, possibly greater than 60% of the fibronectin present in the original plasma fraction.

In contrast to Wallace, the invention of the pending claims relates to a simple, one-step titration process that results in the direct quantitative separation of fibronectin from a plasma solution to yield a purified coagulation factor, in particular a von Willebrand factor (vWF), a process that results in the high yield recovery of 70% to 99%, more preferably at least 90% of the fibronectin present in the plasma fraction. Applicants respectfully submit that the Wallace method cannot be used to extract the high levels of fibronectin required by the pending claims. Thus, in that Wallace fails to disclose each and every element of the claim, Applicants submit that it cannot serve to anticipate the invention of the pending claims. As such, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections of 1-5, 6, 8, 10-11, 14, 16, and 18 under 35 U.S.C. § 102(b) in view of the amendments and remarks herein.

*Rejections under 35 U.S.C. § 103*

*Wallace:*

Claim 7 stands rejected under 35 U.S.C. § 103(a) as being obvious over Wallace et al. (USPN 4,341,764).

According to the Examiner, while Wallace does not expressly teach separation by means of an agitator blade or stirrer, such would have been obvious to one of ordinary skill in the art given the conventional nature of such tools.

Applicants reiterate the arguments above and respectfully submit that Wallace neither discloses nor fairly teaches a high yield process for separating fibronectin from a plasma fraction or producing a coagulation factor composition in which the pH of a plasma fraction containing an initial amount of fibronectin and at least one coagulation factor and characterized by an ionic strength below 500 mM is adjusted to a value between pH 4.7 and pH 5.3 so as to form a precipitate comprising 70% to 99% of the initial amount of fibronectin and a supernatant

containing said at least one coagulation factor. Accordingly, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection of claim 7 under 35 U.S.C. § 102(b) in view of the amendments and remarks herein.

*Burnouf-Radosevich in view of Winkelman:*

Claims 9, 12-13, 15, and 17 stand rejected under 35 U.S.C. § 103(a) as being obvious over Burnouf-Radosevich et al. (USPN 5,408,039, hereinafter referred to as “Burnouf-Radosevich”) in view of Winkelman (USPN 4,789,733, referred to hereinafter as “Winkelman”).

According to the Examiner, Burnouf-Radosevich discloses a process for purifying human von Willebrand factor from a cryoprecipitated plasma fraction that includes the steps of treatment with AIOH to remove fibronectin, treatment with a solvent-detergent to destroy lipid enveloped viruses, and an anion exchange chromatography to yield a vWF eluate contaminated with fibronectin. However, the Examiner admits that Burnouf-Radosevich does not teach precipitation of fibronectin by lower pH. The Examiner cites to Winkelman to cure this deficiency, noting that Winkelman disclose the adjustment of the pH of a blood plasma fraction to below 6.0 to increase the precipitation of fibronectin. The Examiner thus concludes that it would have been obvious to one of ordinary skill in the art to further treat the vWF eluate of Burnouf-Radosevich according to the technique of Winkelman to achieve a purified vWF fraction.

Applicants respectfully disagree, both with the Examiner’s characterization of the prior art teachings and with her conclusion of obviousness. Applicants further submit that the claim amendments presented herewith in order to expedite prosecution render moot the Examiner’s assertion of obviousness.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

In an effort to expedite prosecution, independent claims 1 and 2 have been amended to require the step of adjusting the pH of the plasma fraction to a value between pH 4.7 and pH 5.3. The Examiner expressly admits that Burnouf-Radosevich “do[es] not teach to precipitate fibronectin by lowering the pH”, citing to Winkelman to cure this deficiency. While the Winkelman reference indeed discloses precipitating fibrinogen and fibronectin from a buffered solution of a cryoprecipitate at pH 6-8 by the addition of a sulphated polysaccharide, it does not disclose or suggest the use of lower/acidic pHs, such as those presently claimed. Winkelman observed that while precipitation of fibronectin and fibrinogen tended to increase as pH was reduced, e.g., from pH 7.1 down to pH 5.8, such occurred at the cost of increasing loss of Factor VIII [col. 8: 21-51 (Example 1-7)]. Winkelman thus concluded that Factor VIII has a relatively narrow range of pH stability, being most stable in the neutral pH range of 6.0 to 8.0, more preferably within the range of 6.0 and 7.0, with pH 6.5 being the optimum pH for maximizing Factor VIII recovery [col. 5: 51-64].

Thus, in that neither Burnouf-Radosevich nor Winkelman disclose or suggest the step of adjusting the pH of the plasma fraction to a value between pH 4.7 and pH 5.3 as required by claims 1 and 2 as presently pending, the combination of the two cannot serve to render obvious the invention of the pending claims. As such, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections of claims 9, 12-13, 15, and 17 under 35 U.S.C. § 103(a) in view of the amendments and remarks herein.

### **CONCLUSION**

In view of the foregoing, Applicants respectfully submit that claims 1-18 are in condition and respectfully petition for the early issuance of a Notice of Allowance confirming such.

The Office Action of May 27, 2008 set a three-month shortened statutory period for response. Further to the petition for two-month extension of time submitted herewith, response is due on or before **October 27, 2008**. Accordingly, Applicants submit that this response is timely and no additional fees, apart from those included herewith, are required. However, in the event that further fees are required to enter the instant response and/or maintain the pendency of



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this application, the Commissioner is authorized to charge such fees to our Deposit Account No. 50-2101.

If the Examiner has any questions or concerns regarding this communication, she is invited to contact the undersigned.

Respectfully submitted,

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